Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation

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Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation: Insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial

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Background Patients with atrial fibrillation (AF) are prone to cardiovascular events and anticoagulation-related bleeding complications. We hypothesized that patients with anemia are at increased risk for these outcomes.

Methods We performed a post hoc analysis of the ARISTOTLE trial, which included >18,000 patients with AF randomized to warfarin (target international normalized ratio, 2.0-3.0) or apixaban 5 mg twice daily. Multivariable Cox regression analysis was used to determine if anemia (defined as hemoglobin <13.0 in men and <12.0 g/dL in women) was associated with future stroke, major bleeding, or mortality.

Results Anemia was present at baseline in 12.6% of the ARISTOTLE population. Patients with anemia were older, had higher mean $CHADS_2$ and HAS-BLED scores, and were more likely to have experienced previous bleeding events. Anemia was associated with major bleeding (adjusted hazard ratio [HR], 1.92; 95% CI, 1.62-2.28; $P < .0001$) and all-cause mortality (adjusted HR, 1.68; 95% CI, 1.46-1.93; $P < .0001$) but not stroke or systemic embolism (adjusted HR, 0.92; 95% CI, 0.70-1.21). The benefits of apixaban compared with warfarin on the rates of stroke, mortality, and bleeding events were consistent in patients with and without anemia.

Conclusions Chronic anemia is associated with a higher incidence of bleeding complications and mortality, but not of stroke, in anticoagulated patients with AF. Apixaban is an attractive anticoagulant for stroke prevention in patients with AF with or without anemia. (Am Heart J 2017;185:140-9.)

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Atrial fibrillation (AF) increases the risk of stroke, systemic embolism, and death.[1,2] Oral anticoagulants (OACs) reduce the risk of these outcomes but also increase the risk of bleeding.[3,4] Balancing the clinical benefit for stroke prevention with bleeding is therefore critical.

Anemia is common in patients with AF and may reflect occult bleeding. Indeed, anemia has been identified as a strong predictor of bleeding in anticoagulated patients with AF.[5-11] Anemia also has multiple etiologies unrelated to bleeding and has been associated with an increased incidence of thromboembolic events in several populations,[12-15] including patients with AF.[16]

We hypothesized that anemia is an important comorbidity in patients with AF that is strongly associated with bleeding and stroke and that apixaban will have similar

Table I. Baseline characteristics according to the presence or absence of anemia

Characteristic	Anemia* (n = 2288)	No anemia (n = 15,815)	*P*
Age, median (25th-75th), y	73 (67-79)	69 (62-76)	<.0001
Female sex, no. (%)	803 (35.1%)	5578 (35.3%)	.8705
Systolic BP, median (25th-75th), mm Hg	130 (119-140)	130 (120-140)	<.0001
Heart rate, median (25th-75th), beats/min	74 (64-84)	76 (66-85)	<.0001
Weight, median (25th-75th), kg	78 (65-92)	83 (70-96)	<.0001
Region, n (%)			<.0001
North America	736 (32.2)	3713 (23.5)	
Latin America	323 (14.1)	3114 (19.7)	
Europe	800 (35.0)	6523 (41.2)	
$CHADS_2$ score, mean (SD)	2.4 (1.16)	2.1 (1.09)	<.0001
HAS-BLED score, mean (SD)	2.0 (1.03)	1.7 (1.05)	<.0001
Medical history, n (%)			
Prior stroke or SE	505 (22.1)	3013 (19.1)	.0006
Prior bleeding event	461 (20.1)	2565 (16.2)	<.0001
History of anemia	542 (23.7)	696 (4.4)	<.0001
Hypertension	2017 (88.2)	13,821 (87.4)	.3020
Diabetes	772 (33.7)	3755 (23.7)	<.0001
HF	917 (40.1)	5497 (34.8)	<.0001
CAD	931 (40.7)	5084 (32.2)	<.0001
Renal dysfunction (eGFR <50 mL/min)	737 (32.3)	2260 (14.3)	<.0001
Type of AF			.0163
Paroxysmal	390 (17.0)	2389 (15.1)	
Persistent or permanent	1898 (83.0)	13,423 (84.9)	
Medications at randomization, n (%)			
Prior use of VKAs†	1334 (58.3)	9016 (57.0)	.2420
Aspirin	775 (33.9)	4832 (30.6)	.0013
Clopidogrel	82 (3.6)	254 (1.6)	<.0001
Amiodarone	290 (12.9)	1749 (11.2)	.0223
β-Blocker	1430 (63.5)	9997 (64.2)	.4982
Digoxin	696 (30.9)	5098 (32.8)	.0800
Calcium blocker	741 (32.9)	4801 (30.8)	.0487
Statin	1090 (48.4)	6344 (40.8)	<.0001
NSAID	245 (10.9)	1268 (8.1)	<.0001
Gastric antacid drugs	648 (28.8)	2683 (17.2)	<.0001

P value compares patients with anemia versus no anemia. *BP*, Blood pressure; *SE*, systemic embolism; *HF*, heart failure; *CAD*, coronary artery disease; *eGFR*, estimated glomerular filtration rate; *VKA*, vitamin K antagonist; *NSAID*, nonsteroidal anti-inflammatory drug.
**Anemia* at baseline defined as Hb <13.0 in men and Hb <12.0 g/dL in women.
†Prior use of vitamin K antagonists for >30 consecutive days.

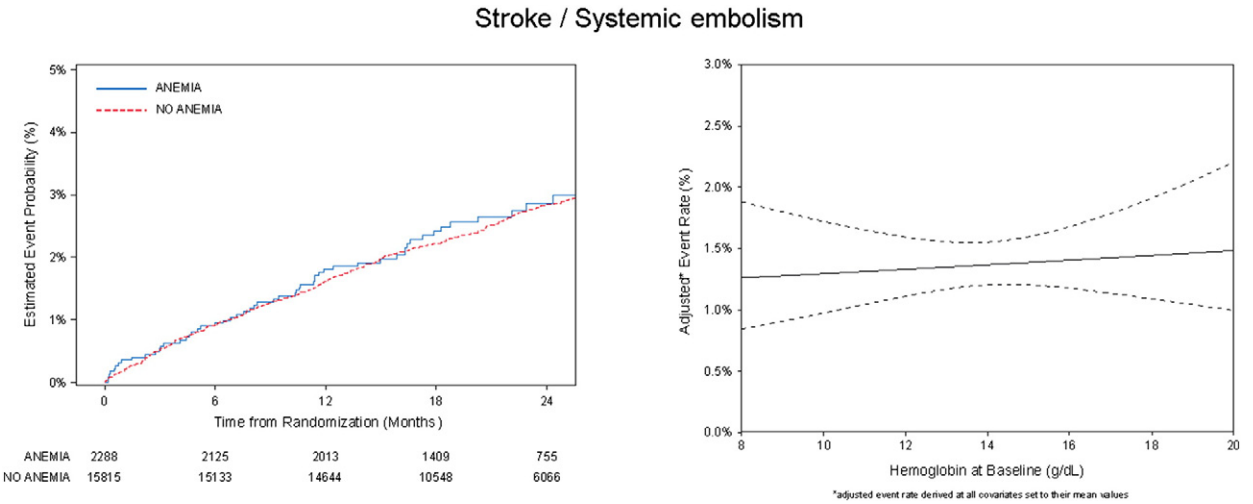
effects in patients with or without anemia. To test our hypotheses, we retrospectively analyzed the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial that included 18,201 patients with AF randomized to dose-adjusted warfarin (target international normalized ratio [INR], 2.0-3.0) or apixaban 5 mg twice daily.[17]

Methods

ARISTOTLE trial design

The ARISTOTLE trial design and the results of the main study have been published previously.[17,18] Briefly, the primary objective of the ARISTOTLE trial was to establish the noninferiority of apixaban 5 mg twice daily compared with warfarin (target INR, 2.0-3.0) for the prevention of stroke or systemic embolism in patients with AF. The ARISTOTLE investigators randomized 18,201 patients with AF and at least 1 additional risk factor for stroke to receive apixaban 5 mg twice daily or dose-adjusted warfarin (target INR, 2.0-3.0) in a double-blind, double-dummy fashion for a median duration of 1.8 years. The primary safety end point was major bleeding defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria. Key secondary end points included whether apixaban provided superior stroke reduction over warfarin, the incidence of major and minor bleeding defined by multiple definitions, the incidence of myocardial infarction, and death from any cause. Key exclusion criteria were AF due to a reversible cause, mitral stenosis, concomitant conditions other than AF that required anticoagulation, an indication for clopidogrel and aspirin, recent stroke, severe renal insufficiency, or severe anemia (hemoglobin [Hb] <9.0 g/dL). All national

Figure 1



Association between anemia and the incidence of stroke or systemic embolism. **A**, Kaplan-Meier analysis of the cumulative incidence of stroke or systemic embolism according to the presence or absence of anemia at baseline. *Anemia* was defined according to the WHO criteria (Hb <13.0 g/dL in men and Hb <12.0 g/dL in women). **B**, Graphic representation of the HR (95% CI) for stroke or systemic embolism according to baseline Hb levels. *Adjusted for age, weight, region, diabetes, hypertension, $CHADS_2$ score, at least moderate valvular heart disease, prior stroke or systemic embolism, type of AF, and prior warfarin use.

regulatory authorities and ethics committees approved the study. All patients provided written informed consent before entry into the study. This study was sponsored by Bristol-Myers Squibb and Pfizer, Inc.

Definition of *anemia*

For the present analysis, we selected patients with Hb values available at baseline. *Anemia* was defined according to the World Health Organization (WHO) criteria (Hb <13.0 g/dL in men and Hb <12.0 g/dL in women). Information about Hb during follow-up was collected every 3 months and was used to define anemia during follow-up using the same criteria.

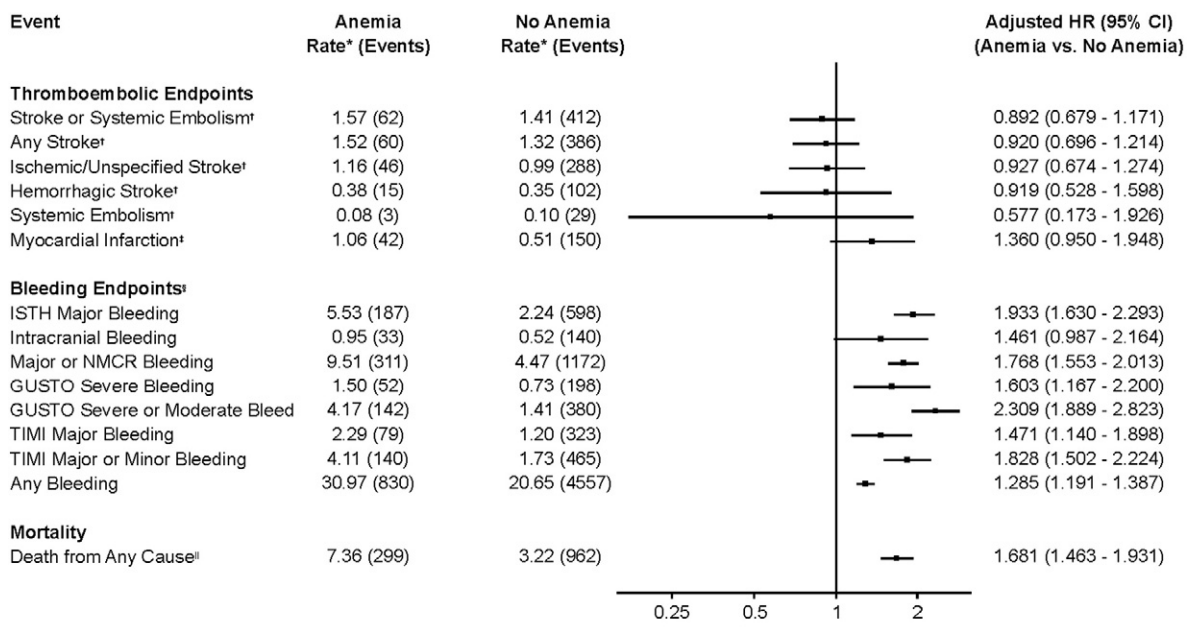
Definitions and outcomes

We focused our analysis on the association between baseline anemia and thromboembolic events or bleeding.[17,18] *Stroke* was defined as a focal neurologic deficit from a nontraumatic cause lasting at least 24 hours and was categorized as ischemic, hemorrhagic, or of uncertain type. *ISTH major bleeding* was defined as clinically overt bleeding accompanied by 1 or more of the following: a decrease in Hb levels of at least 2 g/dL, transfusion of at least 2 U of packed red cells, or bleeding that is fatal or occurs at a critical site. *Clinically relevant nonmajor bleeding* was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy. *Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) major or moderate bleeding* was defined as clinically relevant bleeding that was intracranial, causing severe hemodynamic compromise, or required a transfusion. The *GUSTO minor bleeding* was defined as clinically overt bleeding that did not comply with the definition of GUSTO major or moderate bleeding. *Thrombolysis In Myocardial Infarction (TIMI) major bleeding* was defined as bleeding that was intracranial, causing a cardiac tamponade, or associated with a drop in Hb of >5 g/dL. The *TIMI minor bleeding* was defined as a drop in Hb between 3 and 5 g/dL with an identified bleeding site or when spontaneous gross hemoptysis, hematuria, or hematemesis occurred. Creatinine clearance was estimated using the Cockroft-Gault formula and stratified as normal (>80 mL/min per 1.73 m^2), moderately impaired (between 50 and 80 mL/min per 1.73 m^2), and severely impaired (<50 mL/min per 1.73 m^2).

Statistical analysis

Continuous baseline variables are summarized as medians and 25th and 75th percentiles and compared using the Wilcoxon test. The $CHADS_2$ and HAS-BLED scores are presented as mean and SD and compared using *t* tests. Categorical variables are presented as frequencies and percentages and compared using χ^2 tests. Cumulative event rates according to the presence or absence of anemia were calculated by the Kaplan-Meier method and

Figure 2



*Rates per 100 patient-years of follow-up.
†Adjusted by age, weight, region, diabetes, hypertension, at least moderate valvular heart disease, prior stroke/TIA/systemic embolism, type of AF, and prior VKA use.
‡Adjusted by age, region, diabetes, CAD, history of MI, NYHA class, and renal function.
§Adjusted by age, $CHADS_2$ score, HAS-BLED score, sex, region, CAD, history of MI, history of bleeding, and renal function.
‖Adjusted by age, systolic/diastolic blood pressure, weight, $CHADS_2$ score, sex, region, hypertension, left bundle branch block, history of MI, prior stroke/TIA/systemic embolism, smoking, prior VKA use, NYHA class, and renal function.

Efficacy and safety end points in patients with and without anemia. Forest plots depicting the adjusted HR (95% CI) for the association between anemia and thromboembolic events, bleeding complications, or mortality. *Rates per 100 patient-years of follow-up.

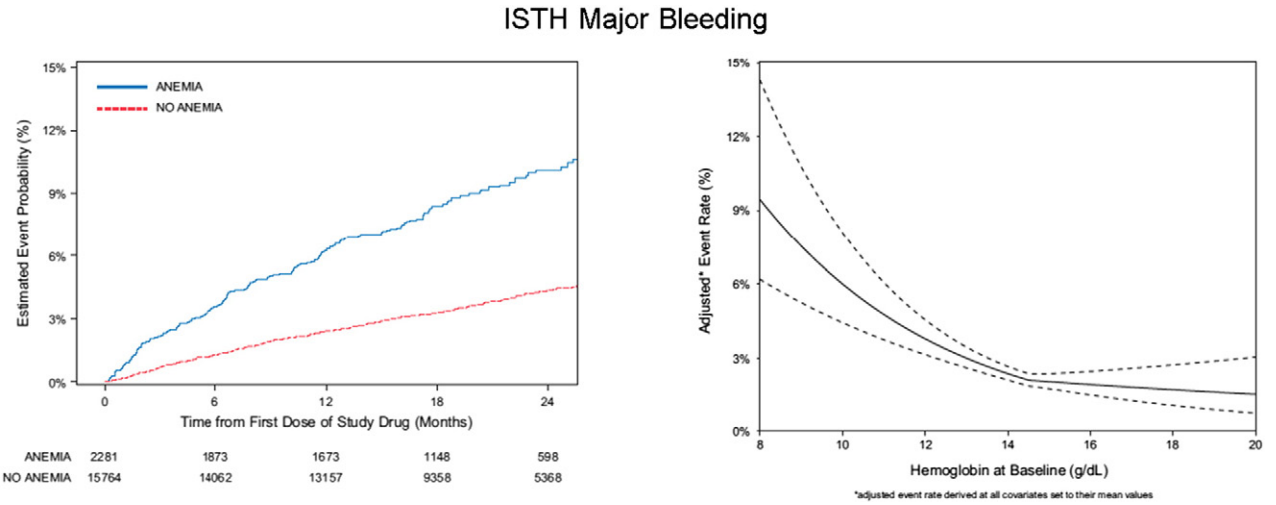
displayed graphically. Characteristics associated with anemia at baseline were identified using a multivariable logistic regression model. Candidate variables for inclusion in the model were sociodemographic characteristics, medical history, and current medications. Continuous variables were tested for linearity using restricted cubic splines and transformed if needed. Variables included in the final model were selected using backward selection algorithm with α level to stay in the model set to .05. The association between anemia or continuous Hb and the incidence of the different outcomes was estimated using a Cox regression model and presented as a hazard ratio (HR) with associated 2-sided 95% CI. Adjusted HRs were derived using a prespecified set of adjustment variables for each individual end point. The interaction between anemia and selected prespecified subgroups (age, sex, $CHADS_2$ and HAS-BLED scores, history of diabetes, coronary artery disease, renal insufficiency, warfarin experience, and history of bleeding) on ISTH major bleeding was additionally explored. Incidence of new anemia was based on Hb levels measured postrandomization. An HR comparing randomized treatments was derived using a parametric model for interval-censored data and assuming a Weibull distribution for the time to new-onset anemia. To determine whether randomized treatment influenced the propensity to develop anemia, the incidence of new-onset anemia was assessed in warfarin-naive patients. Rates of new-onset anemia by randomized treatment were estimated using the parametric model. All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Prevalence of anemia

Of the 18,201 patients randomized in the ARISTOTLE trial, baseline Hb values were available at randomization in 18,103 (99.5%) patients. At that time point, 2,288 (12.5%) patients had anemia according to the WHO criteria. Baseline demographics according to the presence or absence of anemia at randomization are displayed in Table I. In general, patients with anemia were older; had more comorbidities; and had more often experienced prior stroke, systemic embolism, or bleeding events. Both $CHADS_2$ and HAS-BLED scores were significantly higher in patients with anemia.

Figure 3



Association between anemia and the incidence of ISTH major bleeding. **A**, Kaplan-Meier analysis of the cumulative incidence of ISTH major bleeding according to the presence or absence of anemia at baseline. *Anemia* was defined according to the WHO criteria (Hb <13.0 g/dL in men and Hb <12.0 g/dL in women). **B**, Graphic representation of the HR (95% CI) for ISTH major bleeding according to baseline Hb levels. *Adjusted for age, $CHADS_2$ score, HAS-BLED score, sex, region, coronary artery disease, history of myocardial infarction, history of bleeding, and renal function.

Anemia and incidence of thromboembolic events

The incidence of stroke or systemic embolism was comparable between patients with or without baseline anemia (Figures 1, *A*, and 2). There was also no association between Hb considered as a continuous variable and the incidence of stroke or systemic embolism (Figure 1, *B*). Similar results were obtained when stroke, stroke subtype, or systemic embolism was considered separately (Figure 2). The presence of anemia was also not associated with the incidence of future myocardial infarction (Figure 2).

Anemia, bleeding, and mortality

The presence of anemia at baseline was associated with a 1.9-fold higher incidence of ISTH major bleeding events (Figures 2 and 3, *A*). Every 1-mg/dL drop in Hb was associated with a 29% increase in the risk of ISTH major bleeding (Figure 3, *B*). The association between baseline anemia and major bleeding was consistent across multiple bleeding definitions (Figure 2) and several clinically relevant subgroups (Table II). The association between anemia and ISTH major bleeding was stronger in men than in women and also stronger in warfarin-experienced versus warfarin-naive patients. Furthermore, there was a trend toward a stronger association between anemia and bleeding in younger compared with older patients. Baseline anemia was also associated with a 68% increase in all-cause mortality (Figures 2 and 4, *A*). Accordingly, every 1-mg/dL drop in Hb was associated with a 44% increase in the hazard of all-cause mortality (Figure 4, *B*). When this analysis was censored for bleeding reported as cause of death, the results were similar (adjusted HR, 1.551; 95% CI, 1.337-1.799).

Randomized treatment and anemia

The benefits of apixaban over warfarin for the prevention of stroke and bleeding were consistent among patients with and without anemia (Figure 5, *A*, and Table III). New anemia developed in approximately 30% of the warfarin-naive patients during follow-up. The incidence of new-onset anemia was significantly lower in patients randomized to apixaban compared with those randomized to warfarin (HR, 0.91; 95% CI, 0.84-0.98; $P = .037$) (Figure 5, *B*).

Discussion

Anemia has been associated with a large variety of adverse outcomes, ranging from cancer to heart failure hospitalizations.[12-16,19,20] The question therefore arises whether anemia should be considered as a risk factor for an increased bleeding propensity or rather represents a nonspecific comorbidity that is common in vulnerable patients. In patients with AF, anemia has primarily been considered as a predictor of bleeding,[5-11] but recent evidence suggests that it may also predict stroke.[16] In the current analysis of a large contemporary cohort of anticoagulated patients with AF, we confirmed that the presence of anemia is associated with an increased incidence of future bleeding and mortality. In contrast,

Table II. Association between anemia and ISTH major bleeding in prespecified subgroups.

	Anemia	No anemia				
	Rate* (events)	Rate*(events)	Unadjusted HR (95% CI)†	Interaction *P*	Adjusted HR (95% CI)†	Interaction *P*
FV						
<65	3.22 (21)	1.19 (105)	2.660 (1.665-4.250)	.0726	2.113 (1.291-3.458)	.0628
65-75	5.33 (68)	2.04 (216)	2.610 (1.987-3.429)		2.398 (1.809-3.178)	
≥75	6.76 (98)	3.77 (277)	1.773 (1.408-2.233)		1.618 (1.276-2.052)	
Sex						
Male	6.29 (137)	2.15 (378)	2.885 (2.372-3.508)	.0060	2.147 (1.747-2.640)	.0410
Female	416 (50)	2.39 (220)	1.731 (1.273-2.354)		1.474 (1.077-2.018)	
$CHADS_2$ score						
1	4.30 (33)	1.68 (169)	2.556 (1.760-3.713)	.5256	2.139 (1.459-3.137)	.4341
2	5.56 (73)	2.24 (212)	2.472 (1.894-3.225)		2.184 (1.659-2.874)	
≥3	6.24 (81)	3.01 (217)	2.031 (1.573-2.622)		1.654 (1.270-2.153)	
HAS-BLED score						
0-1	3.71 (42)	1.55 (181)	2.377 (1.699-3.326)	.8386	1.813 (1.283-2.562)	.7606
2	5.22 (68)	2.40 (229)	2.163 (1.649-2.835)		1.915 (1.447-2.533)	
≥3	8.15 (77)	3.39 (188)	2.375 (1.822-3.097)		2.163 (1.644-2.846)	
Diabetes						
Yes	6.66 (72)	2.45 (153)	2.672 (2.018-3.537)	.3601	2.323 (1.731-3.117)	.2640
No	5.01 (115)	2.17 (445)	2.288 (1.864-2.809)		1.735 (1.403-2.146)	
Renal impairment						
Severe or moderate	7.24 (73)	4.10 (141)	1.737 (1.309-2.305)	.2923	1.604 (1.203-2.138)	.4292
Mild	5.77 (81)	2.46 (274)	2.348 (1.832-3.008)		2.139 (1.660-2.755)	
No impairment	3.46 (33)	1.49 (180)	2.300 (1.586-3.333)		1.908 (1.305-2.790)	
CAD						
Yes	5.63 (77)	2.04 (176)	2.740 (2.096-3.582)	.3483	2.069 (1.566-2.732)	.5957
No	5.47 (110)	2.33 (422)	2.321 (1.881-2.863)		1.868 (1.504-2.320)	
Warfarin experience						
Naive	4.48 (62)	2.32 (266)	1.891 (1.434-2.494)	.0216	1.445 (1.085-1.924)	.0120
Experienced	6.26 (125)	2.17 (332)	2.879 (2.343-3.537)		2.267 (1.831-2.807)	
History of bleeding						
Yes	8.33 (54)	3.13 (131)	2.643 (1.924-3.630)	.5121	2.301 (1.655-3.198)	.3000
No	4.87 (133)	2.07 (466)	2.335 (1.925-2.831)		1.768 (1.448-2.160)	

*Rates per 100 patient-years of follow-up.
†Hazard ratio is for anemia versus no anemia.

there was no association between anemia and future stroke or other thromboembolic events. These findings therefore indicate that anemia does, indeed, primarily signal an increased bleeding risk and should prompt measures to prevent bleeding. Treatment with apixaban resulted in a reduction in the incidence of new anemia, and apixaban demonstrated similar reductions in stroke and bleeding compared with warfarin in patients with or without anemia at baseline. These findings suggest that apixaban should be preferred over warfarin in patients with AF regardless of whether or not they have anemia.

Anemia in patients with AF

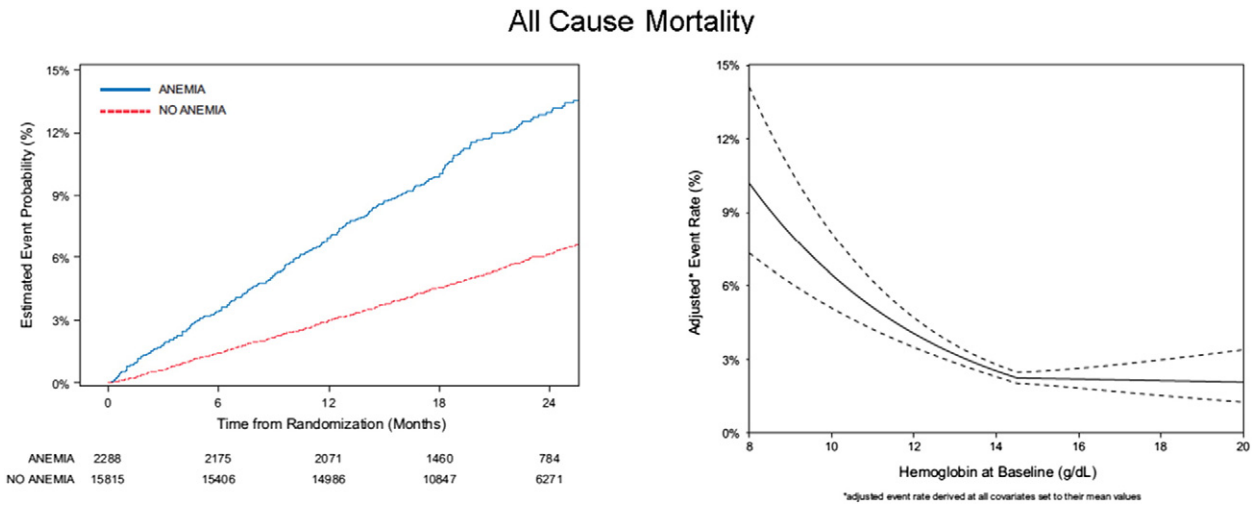
Although the incidence of anemia was relatively low at baseline, one-third of the patients without anemia developed anemia during follow-up. The high incidence and prognostic significance of anemia underscore the fact that it is an important comorbidity in patients with AF that should not be overlooked. Anemia resolved in most patients, suggesting that it was caused by a transient or reversible etiology such as substrate deficiency or bleeding. Nevertheless, the strong association between anemia and mortality may also point toward other concomitant chronic diseases such as renal dysfunction or cancer. Indeed, a recent analysis showed that anemia was a predictor of new malignancies in patients with AF.[16]

Therefore, the association between anemia and bleeding propensity may indicate that anemia is a marker for occult bleeding or general vascular frailty. Alternatively, anemia may represent a surrogate for unrelated comorbidities that predispose to bleeding events. Unfortunately, the design of outcome trials such as ARISTOTLE precludes any meaningful interpretation of the etiology of anemia or the nature of its association with bleeding events.

Anemia and stroke

Anemia is common in patients at an increased risk for stroke, which is underscored by the current analysis

Figure 4



Association between anemia and the incidence of all-cause mortality. **A**, Kaplan-Meier analysis of the cumulative incidence of stroke or systemic embolism according to the presence or absence of anemia at baseline. Anemia was defined according to the WHO criteria (Hb <13.0 in men and Hb <12.0 g/dL in women). **B**, Graphic representation of the HR (95% CI) for all-cause mortality according to baseline Hb levels. *Adjusted for age, systolic and diastolic blood pressure, weight, $CHADS_2$ score, sex, region, hypertension, left bundle-branch block, history of myocardial infarction, prior stroke or systemic embolism, smoking, prior warfarin use, New York Heart Association class, and renal function. *Adjusted event rate was derived with all covariates set to their mean values.

where the $CHADS_2$ score was strongly associated with baseline anemia. Nevertheless, anemia at baseline was not associated with an increased risk of stroke or systemic embolism. Our findings are in contrast with a recent analysis of the RE-LY trial, where anemia was associated with an increased risk of stroke.[16] This may appear contradictory because the inclusion criteria and end points of both trials were very similar.[17,21] However, the association between baseline anemia and bleeding in the RE-LY trial was much stronger than the association between anemia and stroke. Although our analysis cannot exclude that anemia and stroke risk are related, it does underscore the fact that anemia is more strongly associated with bleeding than with stroke.

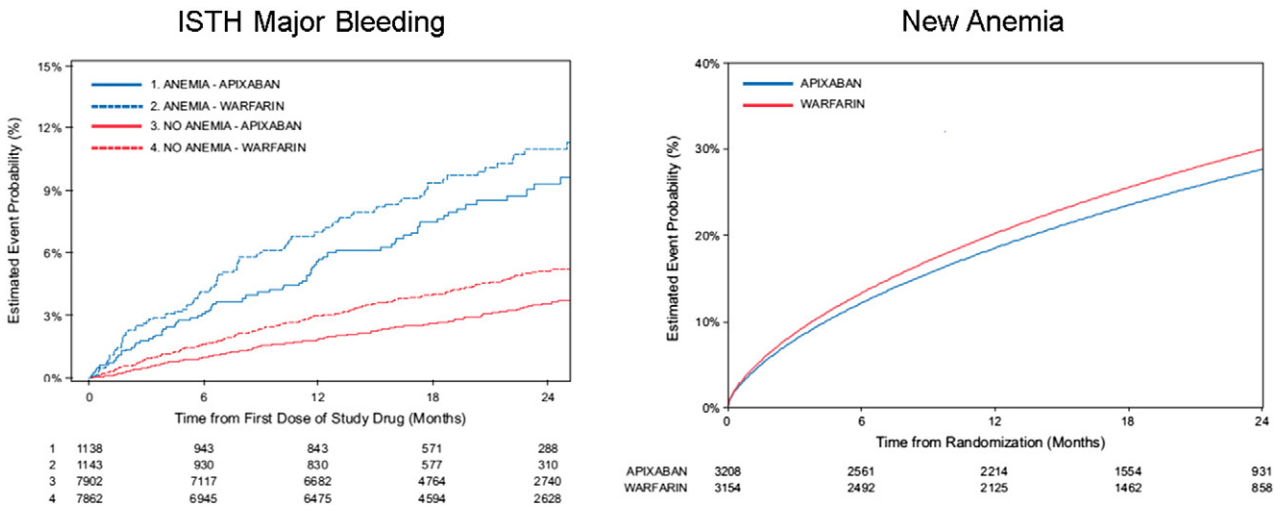
Anemia and bleeding

Oral anticoagulants produce a net clinical benefit in patients at risk for stroke, irrespective of their risk of bleeding.[22-25] Accordingly, guidelines advocate OACs in all patients at risk for stroke.[26] To prevent potentially fatal bleeding events, it is therefore essential to closely monitor patients with a high bleeding risk. However, bleeding risk is generally underestimated by clinicians,[27] and the predictive accuracy of contemporary risk scores is modest.[5,28] There is also considerable overlap between the components of contemporary bleeding risk calculators and stroke prediction algorithms. It would therefore be particularly instrumental to construct algorithms that can differentiate stroke risk from bleeding propensity. In our analysis, the strong and specific association between anemia and bleeding reinforces the notion that anemia should be included in such bleeding risk algorithms.[7,8] Indeed, the addition of Hb and other biomarkers to established clinical predictors in the age, biomarkers, and clinical history risk calculator resulted in superior bleeding risk assessment with only minimal overlap with predictors for stroke.[29]

Clinical implications

The presence of anemia should prompt a detailed diagnostic assessment of the etiology focused on reversible causes. In addition, other reversible factors that may precipitate bleeding such as concomitant antiplatelet or anti-inflammatory drugs, alcohol intake, or uncontrolled hypertension should be addressed.[21] Apixaban reduces the risk for stroke and major bleeding when compared with warfarin, and the current analysis indicates that similar benefits may be expected in patients with anemia.[17] The development of new anemia was also less common in patients randomized to apixaban. Because apixaban reduced the incidence of bleeding, it is tempting to speculate that new-onset anemia reflects differences in recent occult or clinical bleeding events. Unfortunately, the data available in ARISTOTLE preclude any meaningful investigation of the etiology of anemia and cannot provide any temporal associations with prior bleeding. Of the other non–vitamin K antagonist OACs that are currently available, low-dose dabigatran also reduced bleeding compared with warfarin and may be considered in these patients as well; however, low-dose

Figure 5



Effect of randomized treatment on the association between anemia and ISTH major bleeding and on the incidence of new anemia. **A**, Kaplan-Meier analysis of the cumulative incidence of ISTH major bleeding according to anemia status at baseline and randomized treatment. *Anemia* was defined according to the WHO criteria (Hb <13.0 g/dL in men and Hb <12.0 g/dL in women). **B**, New-onset anemia by randomized treatment in warfarin-naive patients. Lines represent HRs for new anemia derived using a parametric model for interval-censored data and assuming a Weibull distribution for the time to new-onset anemia.

dabigatran did not reduce the incidence of new anemia.[16,21]

Limitations

This analysis is from a large data set and includes extensive multivariable adjustments. It is, however, a post hoc analysis, and the potential for confounding remains despite extensive multivariable adjustments. Patients with baseline Hb levels <9 g/dL were excluded from the trial, and the analysis was performed in a population selected according to the ARISTOTLE inclusion criteria. The actual incidence, severity, and prognostic significance of anemia may be different in the general community. The current analysis was also not designed to determine the etiology of anemia.

Conclusions

Anemia is associated with a higher incidence of bleeding and mortality, but not of stroke, in anticoagulated patients with AF. Apixaban has similar benefits over warfarin among patients with and without anemia. Apixaban is therefore an attractive anticoagulant for stroke prevention in patients with AF irrespective of the presence of anemia.

Authorship details

The relative contributions of the authors are as follows: Drs Westenbrink, Alings, and van Gilst contributed to conception and design of the analysis, interpretation of the data, and drafting of the manuscript; Drs Thomas and Wojdyla contributed to analysis and interpretation of the data; Drs Granger, Alexander, Lopes, Hanna, Keltai, Steg, De Caterina, Wallentin, and Hylek designed and conducted the ARISTOTLE trial and contributed to the current analysis by interpretation of the data and critical revision of the manuscript.

Disclosures

Dr Westenbrink received consulting and speaker fees from Boehringer Ingelheim and Bayer and a travel grant from Novartis. Dr Alings received speaker and consulting fees from Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Pfizer, and Sanofi and MSD. Dr Granger received grants and consulting fees from GlaxoSmithKline, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Sanofi-Aventis, The Medicines Company, Janssen, and Bayer; research grants from National Institutes of Health, Food and Drug Administration, Medtronic Foundation, Merck & Co, Novartis, and Armetheon; and consulting fees from Hoffmann-La Roche, Lilly, AstraZeneca, Gilead, and Medtronic. Dr Alexander received institutional research grants from Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Pfizer, Sanofi, Regado Biosciences, Tenax, and Vivus and consulting fees/honoraria from Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, GlaxoSmithKline, Janssen, Pfizer, Portola, Sohmalution, and Xoma. Dr Lopez received institutional research grants from Bristol-Myers Squibb and GlaxoSmithKline and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck,

Table III. Interaction between anemia and randomized treatment

Event	Anemia			No anemia			Interaction *P*
	Apixaban rate* (events)	Warfarin rate* (events)	HR (95% CI)†	Apixaban rate* (events)	Warfarin rate* (events)	HR (95% CI)†	
Efficacy end points							
Stroke or SE	1.13 (22)	2.00 (40)	0.564 (0.335-0.949)	1.28 (188)	1.55 (224)	0.829 (0.683-1.006)	.1692
All-cause mortality	7.51 (151)	7.21 (148)	1.045 (0.833-1.311)	2.99 (448)	3.46 (514)	0.863 (0.760-0.979)	.1503
MI	1.07 (21)	1.05 (21)	1.026 (0.560-1.878)	0.47 (69)	0.55 (81)	0.842 (0.611-1.161)	.5744
Safety end points							
ISTH major bleeding	4.75 (80)	6.32 (107)	0.750 (0.561-1.002)	1.81 (246)	2.67 (352)	0.681 (0.578-0.801)	.5659
GUSTO severe or moderate bleeding	3.06 (52)	5.28 (90)	0.578 (0.411-0.813)	1.07 (146)	1.76 (234)	0.608 (0.494-0.747)	.8058
TIMI major bleeding	1.28 (22)	3.30 (57)	0.387 (0.236-0.633)	0.91 (125)	1.49 (198)	0.615 (0.492-0.770)	.0938
Any bleeding	26.87 (367)	35.24 (463)	0.769 (0.671-0.882)	17.09 (1980)	24.59 (2577)	0.709 (0.669-0.752)	.2941

MI, myocardial infarction.
* Rates per 100 patient-years of follow-up.
† Hazard ratio is for apixaban versus warfarin.

Pfizer, and Portola. Dr Hylek is an advisory board member for Daiichi Sankyo, Janssen, Medtronic, and Pfizer and received lecture fees from and is a board member of Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. Dr Hanna is an employee of Bristol-Myers Squibb. Dr Steg received research grants from Sanofi and Servier; received speaker or consulting fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi, Servier, and The Medicines Company; and owns stocks from Aterovax. Dr De Caterina received honoraria and lecture fees from Bristol-Myers Squibb/Pfizer; is a steering committee member for Bristol-Myers Squibb/Pfizer; received consulting fees and honoraria from Bayer, Merck, and Novartis; and received grant support, consulting fees, and honoraria from Boehringer Ingelheim and Daiichi-Sankyo. Dr Wallentin received research grants from Bristol-Myers Squibb/Pfizer, AstraZeneca, Merck & Co, Boehringer Ingelheim, and GlaxoSmithKline; received honoraria from GlaxoSmithKline; is a member of a consultant/advisory board for Bristol-Myers Squibb/Pfizer, Abbott, AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim; and received travel support/lecture fees from Bristol-Myers Squibb/Pfizer, AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim.

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